DETAILED ACTION

Status of the Application

The remarks and amendments filed on September 25th, 2009 are acknowledged. Claims 1, 4, 9-12, 17, and 27 were amended, and claim 30 was added, claims 1-30 are included in the prosecution.

Response to arguments

Withdrawn Objections/Rejections

Rejection of claims under 35 USC § 103

In view of applicant's amendment of claim 27 the rejection of claims 27-29 under 35 U.S.C. 103(a) as being unpatentable over (Kuzin I. I, et al., Inter. Immun., 12:921-931) is withdrawn.

Maintained Rejections

Rejection of claims under 35 USC § 103

Rejection of claims 1 and 3-14 under 35 U.S.C. 103(a) as being unpatentable over Golub, et al, U.S. Patent 4,666,897 and rejection of claim 2, and claims 15-26 under 35 U.S.C. 103(a) as being unpatentable over Golub, et al, U.S. Patent 4,666,897 as applied to claims 1 and 3-14 above, and further in view of (Joks, et al., J. Allergy Clin. Immunol. 1998, 101:562) are maintained.

Applicant's amendment to claims 1, 4, 9-12, 17 have broadened the scope of the claims rather than narrowed the scope of the claims. The addition of the term "excessive" in instant claim 1 is made in the preamble of the claim.

The recitation of the limitation of "excessive" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See In re Hirao, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and Kropa v. Robie, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

The deletion of "suffering from a disease" changes the patient population of instant claim 1, making it broader. The statement in instant claim 1 of, "comprising administering an IgE lowering effective amount of an antibiotic" is met by administering any antibiotic which lowers IgE concentrations. Given this breadth the previous 103 rejections are maintained for claims 1-26.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 3-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Golub, et al, U.S. Patent 4,666,897.

Claims 1 and 3-14 are drawn to a method for reducing the IgE concentration in the blood of a patient suffering from a disease and administering a therapeutically effective amount of an antibiotic. The antibiotics specifically claimed in claims 1, and claims 3-14 are of the tetracycline family, drawn to the specific antibiotics and mixtures thereof including minocycline, doxycycline, and tetracycline. The prior art teaches the

administration of the antibiotics minocycline, doxycycline, and tetracycline, disclosed on page 7, column 3, paragraph 1. The prior art also discloses on page 6, column 2, lines 40-45 that these antibiotics are used for the treatment of inflammatory associated diseases such as rheumatoid arthritis, and periodontal disease.

Claim 1, and claims 3-14 are drawn to "a method for reducing the IgE concentration in the blood". As both the cited prior art and the claims teach the use of these antibiotics for the treatment of inflammatory diseases, the IgE concentrations of patients must necessarily be reduced in the prior art as well. Thus the current application provides no new information that was not already obvious to one of ordinary skill in the art at the time of the invention.

Though the prior art does not teach the precise mixtures of antibiotics as claimed in claims 6 and 8, it is prima facie obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. In the instant case applicant is making combinations of tetracycline, doxycycline, and minocycline. All of these compounds are known to have similar core structures, are in the same class of antibiotics, and are often substitutes for one another in the treatment of diseases. The idea of combining them flows logically from their having been individually taught in the prior art. In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). **MPEP 2144.06**.

Claims 10, 12, and 13 are drawn to dosages of the drugs ranging from either 1-300 mg/day or 25-100 mg. The prior art teaches on page 7, column 4, line 11, dosage

ranges of 200-500 md/day for tetracycline, and on page 7, column 4, line 29, dosage ranges of 150-900 mg/day for doxycycline.

Claims 9 and 11 are drawn to dosage forms of either paranterally or orally administered forms of the antibiotics. Claim 14 is also drawn to a composition which further comprises a pharmaceutically acceptable carrier. The prior art teaches on page 7, column 4, lines 33-47, the oral and parenteral administration of these antibiotics in the form of "tablets, caplets, or elixirs and the like".

It is also noted for claims 9-13 that it would be routine to optimize the administration form and dosage of the drugs administered depending upon the age of the patient, weight of the patient, the species of animal being treated, the condition being treated, and the severity of said condition. The optimization of the dosage, and dosage form of the drugs administered, and thereby the amounts administered would be obvious to one of ordinary skill in the art at the time of the invention, and therefor would be considered obvious.

Claim 2, and claims 15-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Golub, et al, U.S. Patent 4,666,897 as applied to claims 1 and 3-14 above, and further in view of (Joks, et al., J. Allergy Clin. Immunol. 1998, 101:562).

Claim 2 and claims 15-26 are drawn to a method for reducing the IgE concentration in the blood of a patient suffering from **asthma** and administering a

therapeutically effective amount of an antibiotic. The antibiotics specifically claimed in claims 2, and claims 15-26 are of the tetracycline family, drawn to the specific antibiotics and mixtures thereof including minocycline, doxycycline, and tetracycline. (Golub, et al, U.S. Patent 4,666,897), teaches the administration of the antibiotics minocycline, doxycycline, and tetracycline, disclosed on page 7, column 3, paragraph 1. (Golub, et al, U.S. Patent 4,666,897), also discloses on page 6, column 2, lines 40-45 that these antibiotics are used for the treatment of inflammatory associated diseases such as rheumatoid arthritis, and periodontal disease. (Golub, et al, U.S. Patent 4,666,897), though disclosing the use of tetracycline antibiotics for the treatment of inflammatory diseases, does not specifically disclose the use of these compounds for the treatment of **asthma**. (Joks, et al., J. Allergy Clin. Immunol. 1998, 101:562) teaches on page 562 paragraphs 1 and 2, the use of the tetracycline antibiotic minocycline for the treatment of the inflammatory disease **asthma**. It would therefor have been obvious to one of ordinary skill in the art at the time of the invention to use the common treatment for inflammatory diseases disclosed by (Golub, et al, U.S. Patent 4,666,897) in the treatment of another inflammatory disease asthma, as disclosed by (Joks, et al., J. Allergy Clin. Immunol. 1998, 101:562).

Claim 2, and claims 15-26 are drawn to "a method for reducing the IgE concentration in the blood". As both the cited prior art and the claims teach the use of these antibiotics for the treatment of inflammatory diseases, the IgE concentrations of patients must necessarily be reduced in the prior art as well. Thus the current

application provides no new information that was not already obvious to one of ordinary skill in the art at the time of the invention.

Though the prior art does not teach the precise mixtures of antibiotics as claimed in claims 19 and 20, it is prima facie obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. In the instant case applicant is making combinations of tetracycline, doxycycline, and minocycline. All of these compounds are known to have similar core structures, are in the same class of antibiotics, and are often substitutes for one another in the treatment of diseases. The idea of combining them flows logically from their having been individually taught in the prior art. In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). **MPEP 2144.06**.

Claims 21, 22, 24, and 25 are drawn to dosages of the drugs ranging from either 1-300 mg/day or 25-100 mg. The prior art teaches on page 7, column 4, line 11, dosage ranges of 200-500 md/day for tetracycline, and on page 7, column 4, line 29, dosage ranges of 150-900 mg/day for doxycycline.

Claims 21 and 23 are drawn to dosage forms of either paranterally or orally administered forms of the antibiotics. Claim 26 is also drawn to a composition which further comprises a pharmaceutically acceptable carrier. The prior art teaches on page 7, column 4, lines 33-47, the oral and parenteral administration of these antibiotics in the form of "tablets, caplets, or elixirs and the like".

It is also noted for claims 21-26 that it would be routine to optimize the administration form and dosage of the drugs administered depending upon the age of the patient, weight of the patient, the species of animal being treated, the condition being treated, and the severity of said condition. The optimization of the dosage, and dosage form of the drugs administered, and thereby the amounts administered would be obvious to one of ordinary skill in the art at the time of the invention, and therefor would be considered obvious.

Response to Applicant's Arguments Regarding Above Rejections

Rejection of claims 1 and 3-14 under 35 U.S.C. 103(a) as being unpatentable over Golub, et al, U.S. Patent 4,666,897 and rejection of claim 2, and claims 15-26 under 35 U.S.C. 103(a) as being unpatentable over Golub, et al, U.S. Patent 4,666,897 as applied to claims 1 and 3-14 above, and further in view of (Joks, et al., J. Allergy Clin. Immunol. 1998, 101:562).

Applicant's arguments, starting on page 6, of the reply filed on September 25th, 2009 with respect to the following rejections under 35 USC 103(a) have been fully considered but are not found persuasive:

Applicant argues the following:

1) "There is no teaching in Golub et al. that tetracycline can be used to reduce the excessive circulatory IgE concentration in the plasma of patients. A review of Golub

et al. discloses that there is no mention of any IgE in the document let alone any teaching or suggestion that the antibiotic will lower IgE concentration in the plasma, as claimed. Moreover, the Office Action has not established a recognized nexus between the reduction of collagenic activity and IgE concentrations in the plasma."

2) That Gloub teaches away from the use of tetracyclines for treating inflammatory diseases.

3) That Joks does not teach the use of minocycline to treat asthma, and specifically allergic asthma.

In regards to applicant's argument **1**, the previous office action stated "Claim 1, and claims 3-14 are drawn to "a method for reducing the IgE concentration in the blood". As both the cited prior art and the claims teach the use of these antibiotics for the treatment of inflammatory diseases, the IgE concentrations of patients must necessarily be reduced in the prior art as well."

Both instant claim 1 and the previously rejected claim 1 required the administration of an antibiotic to a patient. The prior art teaches the administration of the claimed antibiotics. By administering such an antibiotic to a patient the IgE concentrations were necessarily lowered, a normal function of the drug. Though no specific reference to this IgE lowering property of the drugs are mentioned by Gloub, it is an inherent property of these drugs. The prior art used also teaches parenteral and oral dosage forms, as stated in the previous office action. As such, the drugs would necessarily be present in the patient's blood and would throughout the body.

"[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). In the instant case, though the drugs were not previous stated to lower IgE levels, it was inherent to their anti-inflammatory function.

In regards to applicant's argument **2**, the section cited suggests the use of tetracyclines in inflammatory diseases such as rheumatoid arthritis and periodontal disease and the disclosure does not criticize, discredit, or otherwise discourage the use of tetracyclines for these diseases. Gloub teaches in claims 1 and 7, the use of tetracyclines to treat rheumatoid arthritis, and in column 9, lines 30 to 53, a patient with gingival inflammation is treated with tetracycline, ameliorating their symptoms. Contrary to applicants statement the reference does teach the use of tetracyclines for inflammatory diseases and does not teach away from their use.

In regards to applicant's argument **3**, that Joks does not teach the use of minocycline to treat asthma, and specifically allergic asthma. The title of the reference is "Minocycline as an anti-inflammatory agent in the treatment of asthma". The reference also recites "Paired t-tests to evaluate ratings of AQLQ (Athma Quality of Life Questionaire) under drug vs. placebo conditions revealed significant improvement in ratings of asthma symptoms in response to environmental stimuli (p=.007) and in

activity limitions (p=.041) with minocycline use.". This statement shows that treatment with minocycline improved symptoms caused by environmental stimuli. Allergic asthma is asthma caused by response to environmental stimuli. The reference teaches the treatment of all types of asthma, and the results of the reference also teach that the treatment was effective for allergic asthma.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 27-29 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "threshold level" in claim 27 is a relative term which renders the claim indefinite. The term "threshold" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The instant specification states in regards to a threshold level "Of a patient suffering from a disease wherein IgE is pathogenic, e.g., allergies or asthma especially allergic asthma, e.g., human allergic asthma, inflammatory conditions and the like can be measured prior to treatment. After a period of treatment, the igE concentration in the plasma is measured

again and the change in the concentration of IgE, if any, is noted. If the concentration of the IgE in the plasma **is above a threshold level determined by the physician** and is not decreased, then the physician should change the treatment regimen and prescribe a greater dose of tetracyclines for the treatment of the disease." Thus a threshold level is an indefinite term, as it is dependent upon a determination made by a clinician as well as a number of factors such as the type of disease being treated, the progression of the disease, the size of the patient, the current state of the patient, etc. Thus the scope of the instant claims is indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1- 5, 9, and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by (Joks, et al., J. Allergy Clin. Immunol. 1998, 101:562).

Claims 1-5, 9, and 10 are rejected given the currently broadened scope of instant claim 1. Joks teaches the use of the tetracycline antibiotic minocycline for the treatment of the inflammatory disease asthma and shows evidence for treating allergic asthma (showing that the treatment improves the patient's response to environmental stimuli). Minocycline is orally administered at 150 mg/day. See on page 562 paragraphs 1 and 2. The administration of minocycline inherently lowers the IgE concentration of the patients

reading on the limitation of an IgE lowering effective amount as recited in instant claim 1. The antibiotic minocycline reads on the antibiotic of instant claims 1-5, 9, and 10. The dosage of 150 mg/day reads on the range of 1 to 300 mg/day recited in instant claim 10.

Claim 27 is rejected under 35 U.S.C. 102(b) as being anticipated by Ricketti, A.J., et al., (Journal of Allergy and Clinical Immunology, 1984).

Ricketti teaches testing the IgE levels of human (mammalian) patients with allergic bronchopulmonary aspergillosis, which reads on a disease in which IgE is pathogenic. The patients' serum IgE levels were tested upon their initial presentation to the study. The patients were administered a drug (corticosteroid therapy), which lowered their IgE levels. The patients IgE levels were tested on a monthly or bimonthly basis during treatment. See paragraph 4, page 69. The values of the first and second determination were compared. See table 1.

The limitation in instant claim 27 of "wherein if the value of the second determination of the free IgE level is higher than or about the same as the first determination and above a threshold level, then the dosage amount of the drug is increased" is a step that has two alternatives, either maintaining or increasing the dosage of a drug. Ricketti teaches all of the prior active steps of instant claim 27. The patients in this study showed a lowering of their IgE concentrations indicating that the concentration of the drugs used were should not be increased. This treatment follows the second option inherently presented by the instant claim, maintaining the level of the drug being administered. Rickette inherently meets all of the limitations of instant claim 27.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 27-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ricketti, A.J., et al., (Journal of Allergy and Clinical Immunology, 1984) in view of Hughes, C.E., et al., (Antimicrobial Agents in Chemotherapy, 1984)

Ricketti teaches a method to monitor the effects of a drug treatment upon allergic bronchopulmonary aspergillosis patients by monitoring their IgE levels as stated above. Ricketti also shows that positive cultures of Aspergillus fumigatus, the cause of allergic bronchopulmonary aspergillosis are often found in ABPA patients. See page 71, paragraph 1.

Ricketti does not disclose monitoring the effectiveness of a tetracycline such as minocycline or doxycycline.

Hughes teaches the use of a mixture of Amphotericin B and tetracycline analogs (minocycline) as an antifungal treatment for aspergillus species, such as A. fumigatus, the cause of allergic bronchopulmonary aspergillosis. See abstract.

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to substitute one treatment for a disease caused by Aspergillus fumigatus with another treatment for a disease caused by Aspergillus fumigatus in a method used to monitor the effectiveness of such treatments. The substitution of Amphotericin B and minocycline (used to kill aspergilllus fumigatus, the cause of allergic bronchopulmonary aspergillosis) for the prednisone (used to treat allergic bronchopulmonary aspergillosis) taught by Rickette would have allowed a physician to monitor the effectiveness of another treatment for allergic bronchopulmonary

aspergillosis. The teachings of Rickette suggest using serum IgE as a general aid to monitor the management of allergic bronchopulmonary aspergillosis. A mixture of Amphotericin B and minocycline is merely another equivalent treatment for managing allergic bronchopulmonary aspergillosis.

Claim 30 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fahy, J.V., et al., (Clinical and Experimental Allergy, 2000) in view of Kuzin, I.I., et al., (International Immunology, 2001).

Fahy teaches the treatment of asthma patients by reducing IgE levels using an antibody drug. Fahy teaches measuring the amount of IgE levels in a patient's serum. It is stated that IgE levels, upon treatment, need to be undetectable, or nearly so, requiring a dosage high enough to reduce the IgE levels to less than 100 Iu/ml. See page 17, paragraph 6, and the title of cited reference 20.

Fahy does not teach the use of an antibiotic to reduce the IgE levels in patients.

Kuzin, I.I., et al., teaches that doxycycline (an antibiotic) is a drug which reduces IgE levels. See figures 1, 2, and page 928.

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to substitute one IgE lowering drug for another IgE lowering drug in a treatment designed to lower IgE levels. Both the antibody drugs of Fahy and the antibiotic doxycycline of Kuzin are merely art known equivalents for lowering IgE concentrations.

Conclusion

No claims allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LANCE RIDER whose telephone number is (571)270-1337. The examiner can normally be reached on M-F 11-12 and 1-4.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571)272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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